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A Novel Approach to Treatment Resistant Depression: Esketamine

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Disclosures

- Dr. Ehret does not have financial or other relationship with the manufacturer(s) of any commercial product(s) or provider(s) of any commercial service(s) discussed in this activity
- This presentation will include discussion of off-label, experimental, and/or investigational use of drugs or devices: esketamine use for major depression with active suicidal ideation

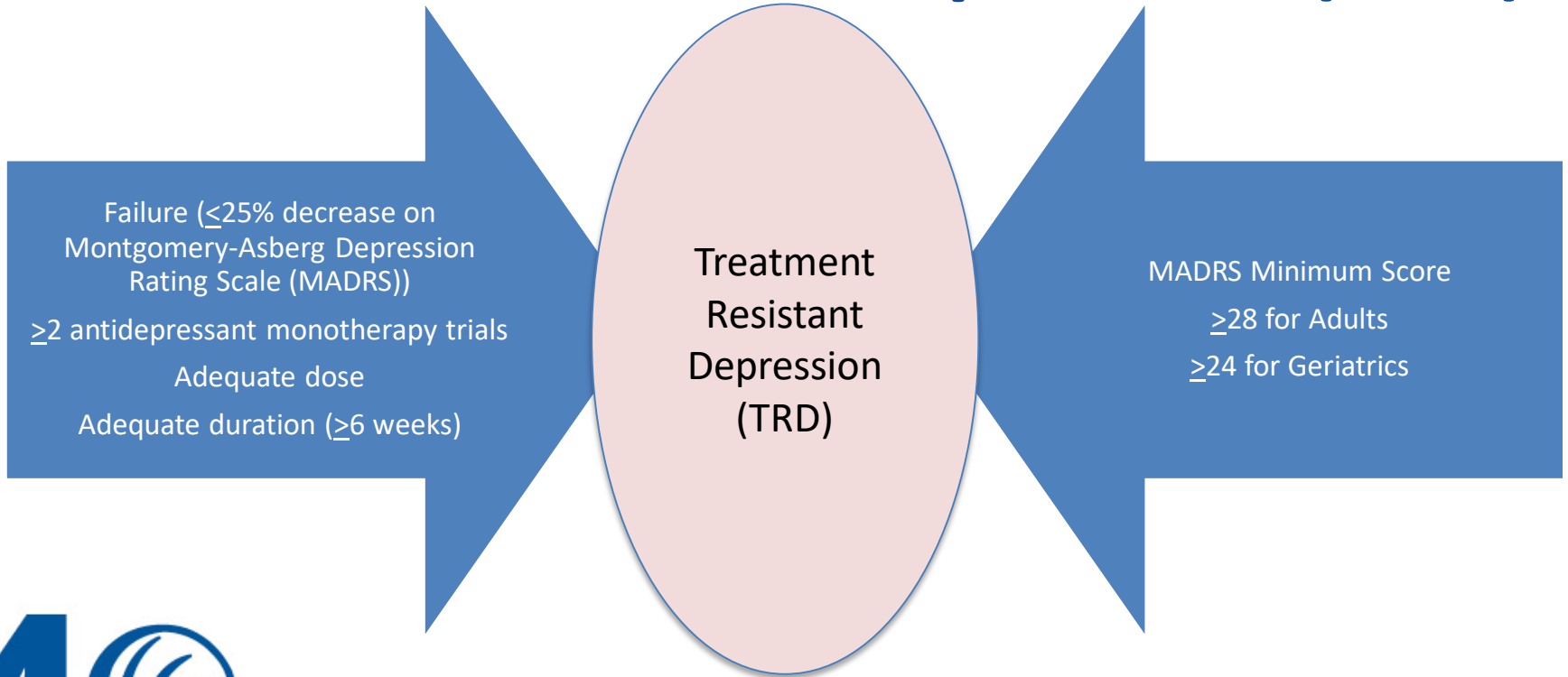


Objectives

- List the current treatments that may be used to help individuals with treatment-resistant depression
- Describe the mechanism of action of esketamine
- Discuss the benefits, risks, and the appropriate use of esketamine



Treatment Resistant Depression (TRD)



Therapeutic Options for TRD

- Augmentation
 - Addition of a second medication
 - Lithium
 - Thyroid hormone
 - Second-generation antipsychotics



Therapeutic Options for TRD

- Stimulants
- Optimizing, combining, and switching classes of antidepressant pharmacotherapy
- Psychotherapy



Therapeutic Options for TRD

- Electroconvulsive Therapy
 - Best therapeutic option for TRD
- Repetitive Transcranial Magnetic Stimulation
- Vagus Nerve Stimulation



Novel Therapeutics for TRD

- Ketamine
- Psilocybin
 - Partial serotonin receptor agonist



Esketamine



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Mechanism of Action

- Non-competitive N-methyl D-aspartate (NMDA) receptor antagonist
- S-enantiomer of racemic ketamine, a non-selective, non-competitive antagonist of the NMDA receptor, an ionotropic glutamate receptor



Formulary Process: Esketamine Nasal Spray

- Indication: Treatment-resistant depression; available only at a certified prescriber's office or clinic
- New Drug Application to FDA Oct. 2019: Rapid reduction of depressive symptoms in adults with major depression with active suicidal ideation intent

FDA News Release: FDA approves new nasal spray medication for treatment-resistant depression;

<https://www.fda.gov/news-events/press-announcements/fda-approves-new-nasal-spray-medication-treatment-resistant-depression-available-only-certified>



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Esketamine REMS

- Healthcare setting and administered to patients enrolled in the program
- Administered by patients under the direct observation of a healthcare provider
- Monitored for at least two hours after administration



Esketamine [Package Insert]. Janssen Pharmaceuticals Inc. Titusville, NJ; 3/19

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Esketamine Contraindications

- Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels arteriovenous malformation)
- History of intracerebral hemorrhage
- Hypersensitivity to esketamine, ketamine, or to any of the excipients



Boxed Warning on Esketamine

Product Label

Sedation & Dissociation

- Patients must be monitored ≥ 2 hours after each treatment
- Must be assessed as clinically stable and ready to leave

Abuse and Misuse

- Assessment of risks and benefits
- Monitor during treatment

Risk Evaluation and Mitigation Strategy (REMS)

- Requires training and participation
- Esketamine REMS

Suicidal Thoughts and Behaviors

Not Approved in Pediatric Patients



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Recommended Dosage for Esketamine

(Dosage adjustments should be made based on efficacy and tolerability)

Adults

Induction Phase[†]

Weeks 1-4:

Day 1 starting dose: 56 mg

Administer twice per week

Subsequent doses: 56 mg or 84 mg

Maintenance Phase

Weeks 5-8:

Administer once weekly

56 mg or 84 mg

Week 9 and after:

Administer every 2 weeks or once weekly[‡]

56 mg or 84 mg

[†] Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine need for continued treatment

[‡] Dosing frequency should be individualized to the lowest frequency to maintain remission/response.

Considerations for Use

- Inpatient versus outpatient
- Medical or pharmacy benefit
- Process for procurement and delivery to administration site
- Completion of REMS enrollment forms
- Location of administration

Logistics of the Clinic

- Prior Authorization
 - Induction
 - Maintenance
 - Continuation of treatment?

Checklist Prior to Scheduling

- Confirmed diagnosis of MDD
- At least 2 trials of antidepressants at max. tolerated dose and adequate duration
- Verified insurance coverage and payment
- Reviewed esketamine medication guide
- REMS enrollment form
- Development of spray and visit schedule with provider (8 weeks)
- Reminder phone calls
- Verify arranged transportation
- Pregnancy screening and prevention
- Urine drug screening



Drug Interactions

- CNS Depressants: may increase sedation
- Psychostimulants: may increase blood pressure
- Monoamine oxidase inhibitors: may increase blood pressure



Esketamine [Package Insert]. Janssen Pharmaceuticals Inc. Titusville, NJ; 3/19

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Administration of Esketamine

- Should be administered in conjunction with an oral antidepressant

Under the supervision of a health care provider, patients will self-administer the following number of devices, with a 5-minute rest between use of each device

- 2 devices (for a 56 mg dose)
- 3 devices (for an 84 mg dose)



Considerations Prior to Initiating and During Therapy

- Blood pressure
 - >140/90- consideration of risks vs. benefits
 - After dosing, reassess blood pressure at ~40 minutes and subsequently as clinically warranted
 - If blood pressure is decreasing and patient appears clinically stable- patient can be discharged



Day of Administration

Food and Liquid Intake:

Because some patients may experience nausea and vomiting after administration of esketamine, advise patients to avoid food for at least **2 hours** before administration and to avoid drinking liquids at least **30 minutes** prior to administration.

Nasal Corticosteroid or Nasal Decongestant:



Patients who require a nasal corticosteroid or nasal decongestant on a dosing day should administer these medications at least 1 hour before esketamine.



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Step 1: Get Ready

Before first device only:



Instruct patient to blow nose **before first device only**.

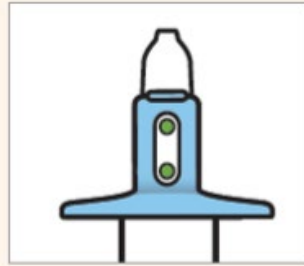


Confirm required number of devices.

56 mg = 2 devices

84 mg = 3 devices

Step 2: Prepare Device



Healthcare professional:

- **Do not prime device.** This will result in a loss of medication.
- Check that indicator shows **2 green dots**. If not, dispose of device and get a new one.
- Hand device to patient.

Indicator

One device contains 2 sprays.
(1 spray for each nostril)

2 green dots (0 mg delivered)



Device full

1 green dot



One spray delivered

No green dots (28 mg delivered)



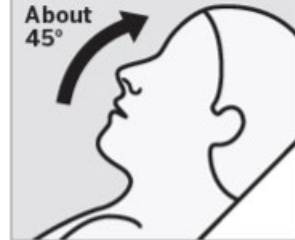
Device empty



Patient should:

- Hold device as shown with the thumb gently supporting the plunger.
- **Do not** press the plunger.

Step 3: Prepare Patient



Patient should:

- Recline head at about **45 degrees** during administration to keep medication inside the nose.



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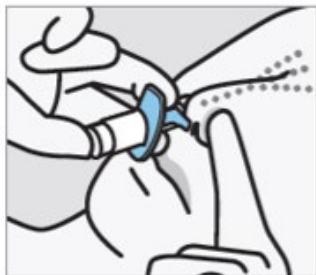
Esketamine [Package Insert]. Janssen Pharmaceuticals Inc. Titusville, NJ; 3/19

Step 4:
Patient
Sprays
Once into
Each
Nostril



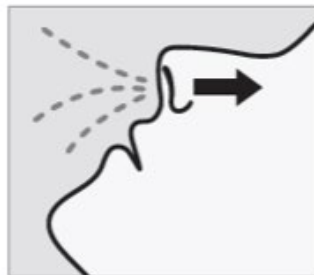
Patient should:

- Insert tip straight into the **first nostril**.
- Nose rest should touch the **skin between the nostrils**.



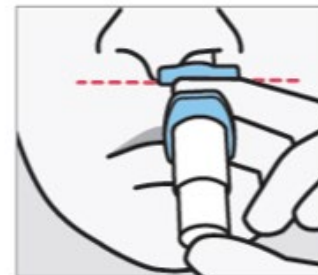
Patient should:

- Close opposite nostril.
- **Breathe in through nose** while pushing plunger all the way up until it stops.



Patient should:

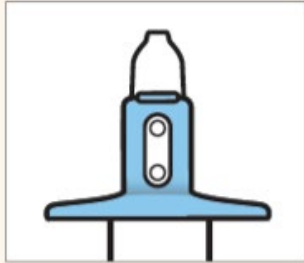
- **Sniff gently** after spraying to keep medication inside nose.



Patient should:

- Switch hands to insert tip into the **second nostril**.
- Repeat Step 4 to deliver second spray.

Step 5: Confirm Delivery and Rest




Healthcare professional:

- Take device from patient.
- **Check that indicator shows no green dots.** If you see a green dot, have patient spray again into the second nostril.
- Check indicator again to confirm device is empty.



Patient should:

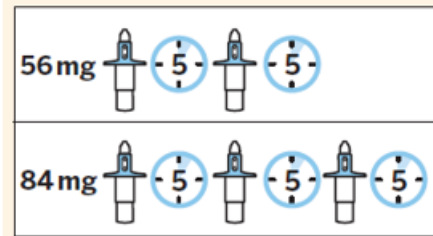
- Rest in a comfortable position (preferably, semi-reclined) for **5 minutes after each device.**
- If liquid drips out, dab nose with a tissue.

 **Do not blow nose.**

Next Device if
Required

Disposal

Dispose of used device(s) per facility procedure for a Schedule III drug product and per applicable federal, state, and local regulations.



Healthcare professional:

Repeat Steps 2-5 for the next device.

IMPORTANT: Ensure that patient **waits 5 minutes after each device** to allow medication to absorb.



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Post Administration

- During and after administration at each treatment session, the patient must be observed for at least 2 hours until the patient is safe to leave

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Missed Treatment Session

- Consider returning to the patient's previous dosing schedule (i.e., every two weeks to once weekly, weekly to twice weekly)
- Consideration of returning to clinic



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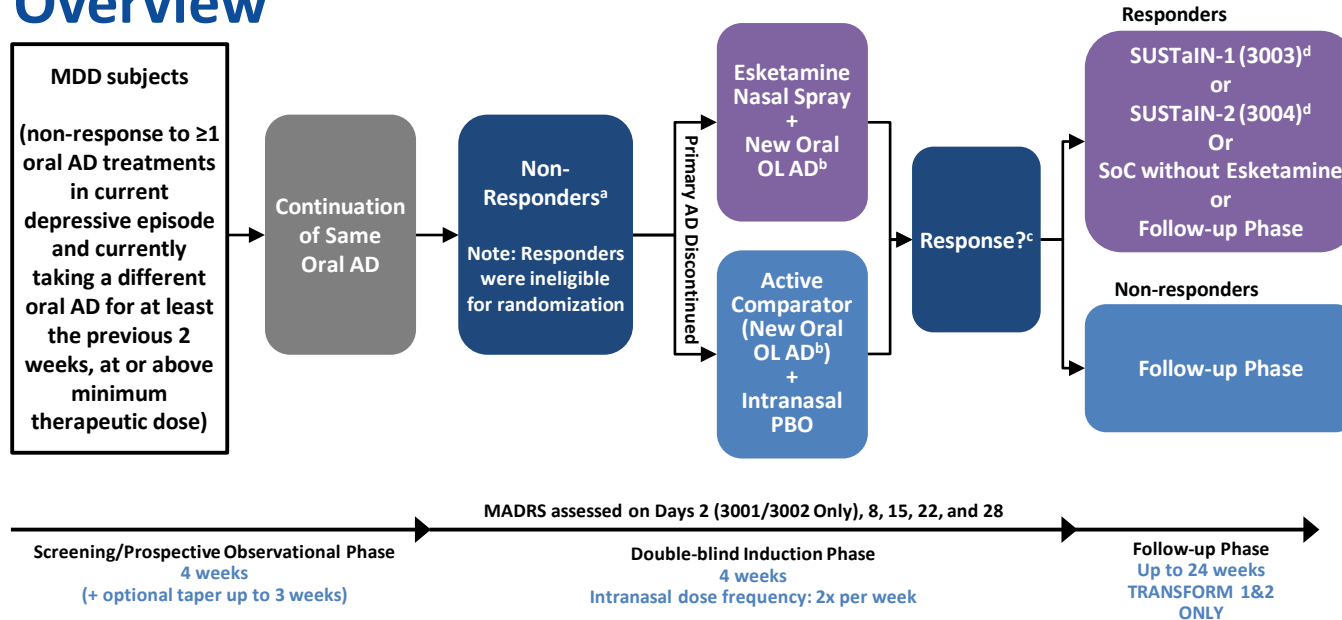
TRANSFORM-1 (3001), TRANSFORM-2 (3002) & TRANSFORM-3 (3005)

Short-Term Studies



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TRANSFORM (3001¹, 3002², and 3005³) Short-Term Study Design Overview



AD, antidepressant; MADRS, Montgomery-Asberg depression Rating Scale; MDD, major depressive disorder; OL, open label; PBO, placebo.

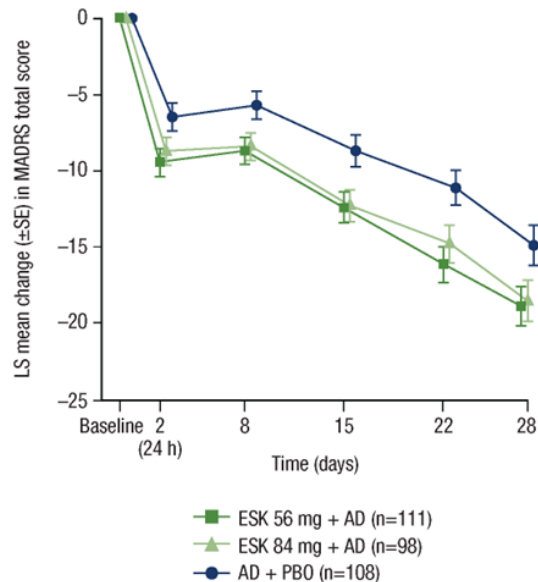
a. Non-response at end of screening (3001 and 3002) = $\leq 25\%$ improvement in MADRS total score from week 1 to week 4 and a MADRS total score ≥ 28 at weeks 2 and 4; Non-response at end of screening (3005) = $\leq 25\%$ improvement in MADRS total score from week 1 to week 4 and a MADRS total score of ≥ 24 at weeks 2 and 4.

b. Oral antidepressants included: duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR]

c. Responder = $\geq 50\%$ reduction in the MADRS total score from baseline (day 1 pre-randomization) to the end of the double-blind phase.

d. Responders in TRANSFORM-1 (3001)/TRANSFORM-2 (3002) could enter SUSTaIN-1 (3003) or follow-up phase; Regardless of response in TRANSFORM-3 (3005) patients could enter SUSTaIN-2 (3004) or follow-up phase.

LS Mean Change in MADRS Total Score Over Time in Double-blind Phase



MADRS Total Score (Difference in LS Mean vs placebo at day 28):

Esketamine 56 mg + oral AD: -4.1
Esketamine 84 mg + oral AD: -3.2

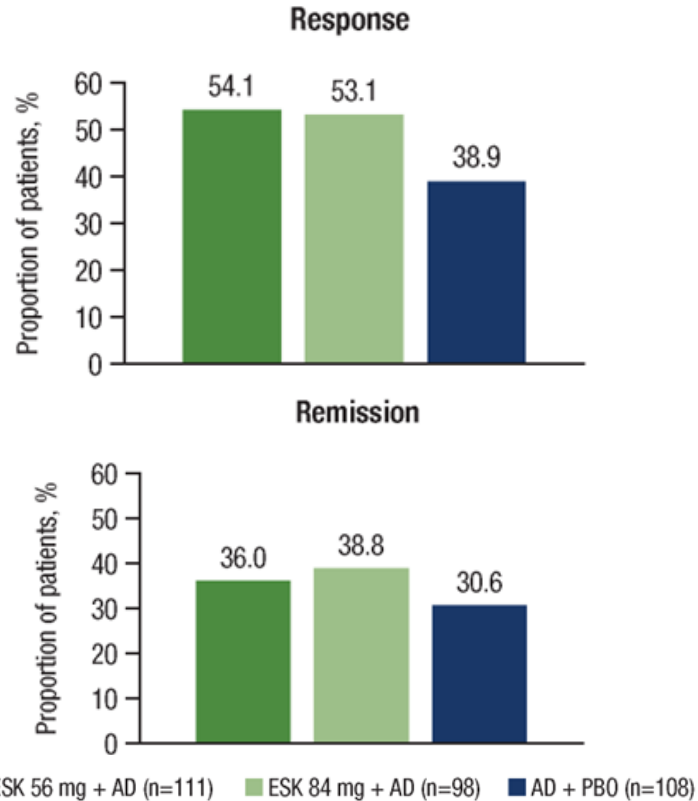
ESK: esketamine; LS: least squares; MADRS: Montgomery-Asberg Depression Rating Scale; SE: standard error

Both ESK + oral AD groups (ESK 56 mg and 84 mg) showed a clinically meaningful and numerically greater change from baseline to day 28 in mean MADRS total score compared to AD + PBO (-19.0 vs. -18.8 vs. -14.8, respectively).

However, statistical significance was not demonstrated with the 84 mg ESK + AD group (95% CI: -6.88, 0.45; $P=0.088$); therefore, 56 mg ESK + AD (95% CI: -7.67, -0.49; $P=N/A$), as well as other secondary endpoints, could not be formally evaluated.

Response and Remission Rates at Study Endpoint (Day 28)- 3001

Response and remission rates were numerically greater with esketamine + oral AD (56 mg and 84 mg) groups vs oral AD plus placebo nasal spray.



Response: $\geq 50\%$ improvement on MADRS from Baseline; Remission: MADRS Total Score ≤ 12

Primary Endpoint 3002

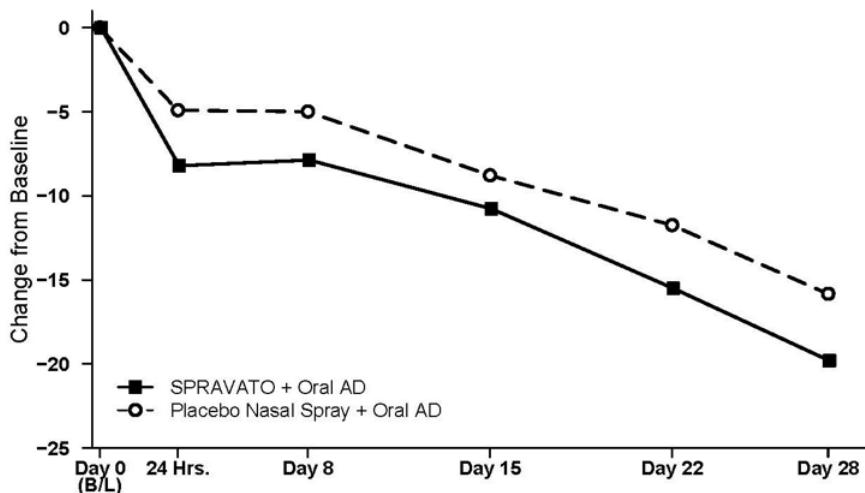
Esketamine + oral AD group showed a greater improvement from baseline to day 28 in mean MADRS total score compared to the oral AD + placebo group.

Most of esketamine's treatment difference (compared to placebo) was observed at 24 hours ($P=0.321$).

Between 24 hours and Day 28, there was continued improvement in both treatment groups: the difference between the groups generally remained but did not appear to increase over time through Day 28.

At day 28, 67% of patients randomized to esketamine were on 84 mg.

LS Mean Change in MADRS Total Score Over Time in Double-blind Phase²



Note: In this flexible-dose study, dosing was individualized based on efficacy and tolerability. Few subjects (<10%) had reduction in SPRAVATO™ dosage from 84 mg to 56 mg twice weekly.

MADRS Total Score (LS Mean Change from Baseline to end of week 4):

²Esketamine (56 mg or 84 mg) + oral AD: -19.8
oral AD + Placebo Nasal Spray: -15.8

LS Mean difference: -4.0
(95% CI: -7.3, -0.6)

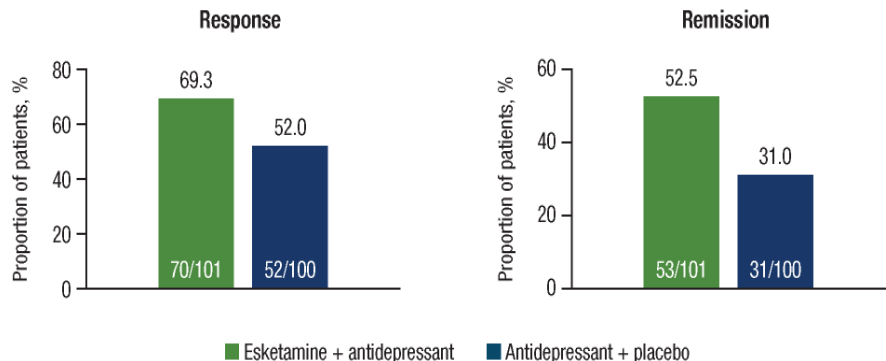
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1. Popova V, Daly EJ, Trivedi M, et al. Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomized double-blind active-controlled study. [published online ahead of print May 21, 2019]. *Am J Psychiatry*. doi:10.1176/appi.ajp.2019.19020172. 2. SPRAVATO™ Prescribing Information

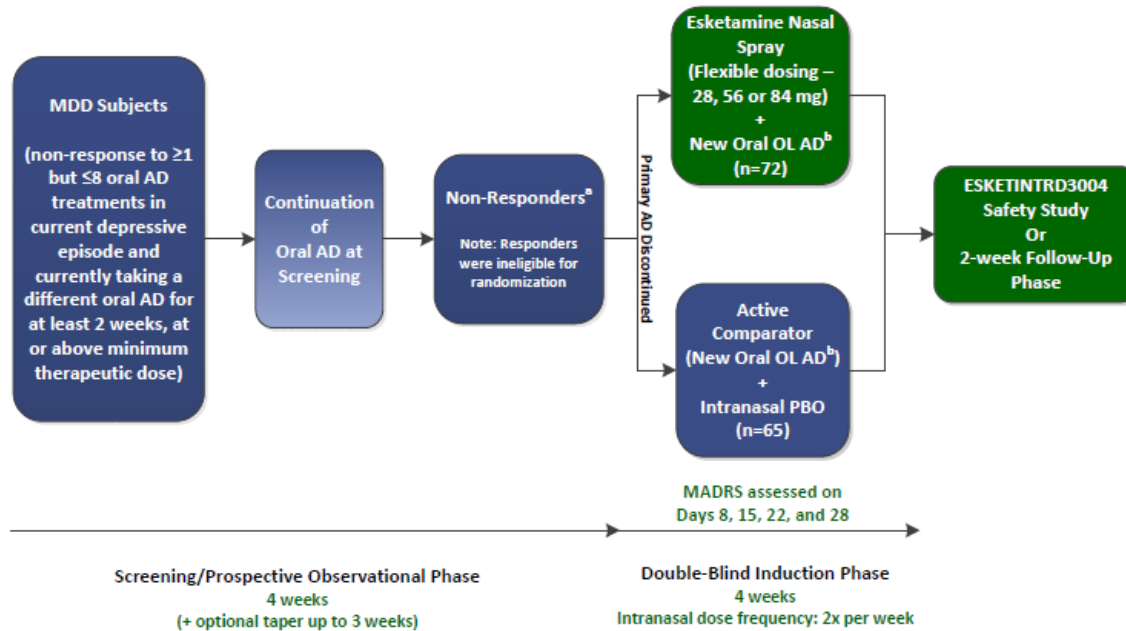
Response and Remission Rates at Study Endpoint (Day 28)- 3002

A greater proportion of patients treated with esketamine + oral AD demonstrated response and were in remission at the end of the 4-week double-blind induction phase than for oral AD plus placebo nasal spray.



Response: $\geq 50\%$ improvement on MADRS from Baseline; Remission: MADRS Total Score ≤ 12

TRANSFORM-3 (3005) Study

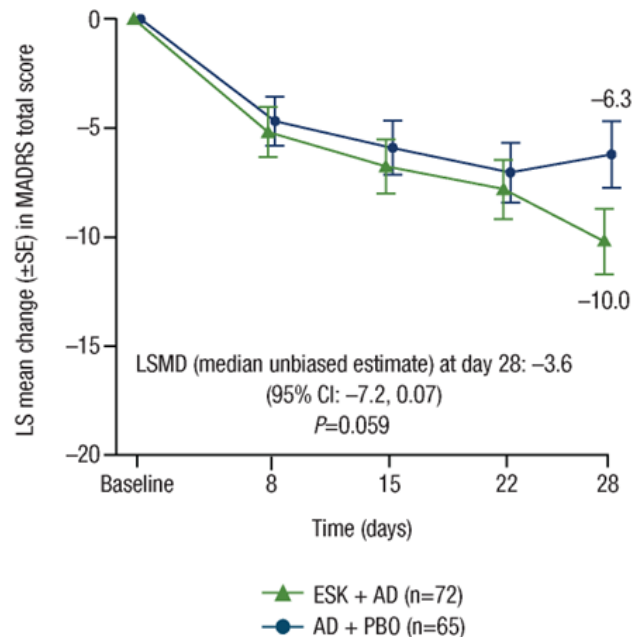


Abbreviations: AD, antidepressant; MADRS, Montgomery-Asberg depression Rating Scale; MDD, major depressive disorder; OL, open-label; PBO, placebo
a. Non-response at end of screening = $\leq 25\%$ improvement in MADRS total score from week 1 to week 4 and a MADRS total score ≥ 24 at weeks 2 and 4
b. Oral antidepressants included: duloxetine, escitalopram, sertraline, or venlafaxine extended release [XR]

Primary Endpoint- 3005

While not statistically significant, the ESK + oral AD group showed a numerically greater improvement in the MADRS total score from baseline to day 28 compared to the oral AD + PBO group.

LS Mean Change in MADRS Total Score Over Time in Elderly Patients



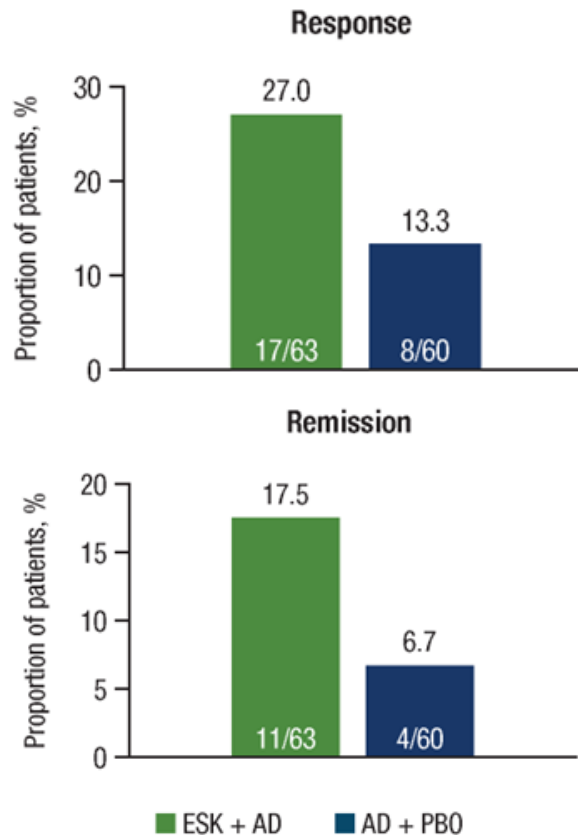
Median unbiased LS difference estimate between esketamine nasal spray + oral AD vs placebo nasal spray + oral AD at Day 28:

Total Study Population: -3.6 ($P=0.059$)

Response and Remission Rates at Study Endpoint (Day 28)

Overall response rates at day 28 favored the intranasal ESK + oral AD group (17 of 63 [27.0%] subjects) compared with the oral AD + PBO group (8 of 60 [13.3%] subjects).

At Day 28, 11 of 63 (17.5%) subjects in the ESK + oral AD group and 4 of 60 (6.7%) subjects in the oral AD + PBO group were in remission.



Summary

Short-Term Studies

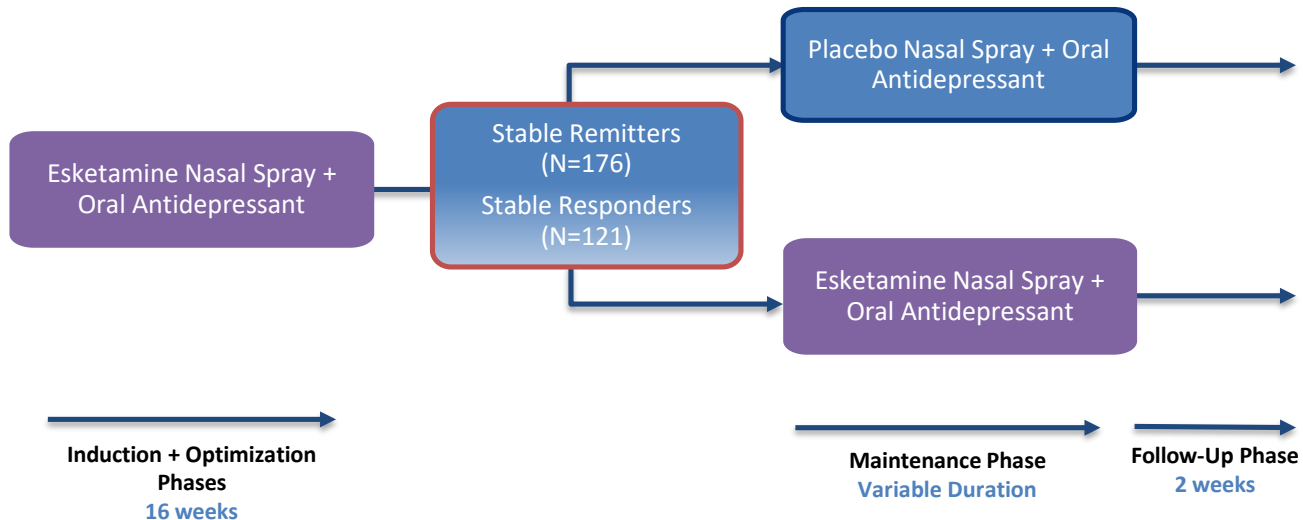
- ✓ In study 3002 (18-64 years population), esketamine nasal spray (NS) plus a newly initiated oral antidepressant (AD) resulted in clinically meaningful^{1,2} and statistically significantly greater improvement in depressive symptoms compared with standard of care (oral AD) plus placebo. Adverse events were predominately seen on the day of dosing, were transient and the majority resolved within 90 minutes of dosing.³
- ✓ In study 3001, fixed-doses of esketamine (56 mg and 84 mg) plus oral AD demonstrated a clinically meaningful^{1,2} treatment benefit in the improvement of depressive symptoms in adults with TRD compared to a new oral AD plus placebo, but did not reach statistical significance.⁴
- ✓ In study 3005 (≥ 65 years population), a clinically meaningful treatment difference in MADRS total score change from baseline to the end of the 4-week induction phase favored esketamine plus a newly initiated oral AD compared with standard of care (oral AD) plus placebo. Safety profile was consistent with that observed in a younger adult population.⁵

SUSTAIN-1 (3003) & SUSTAIN-2 (3004)

Long-Term Studies



SUSTAIN-1 (3003) Study Design

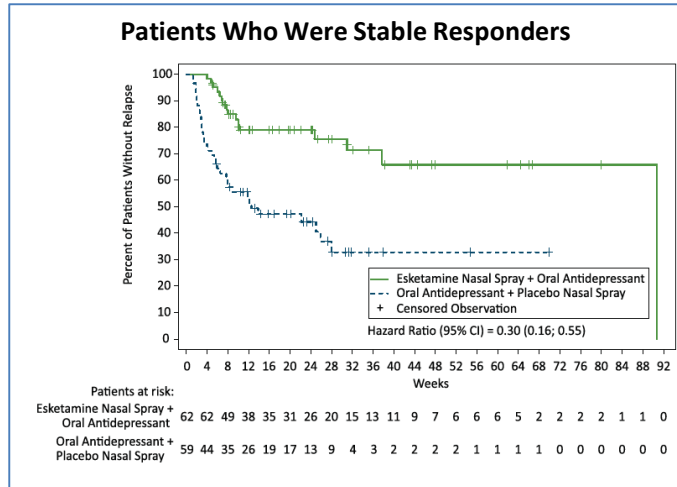
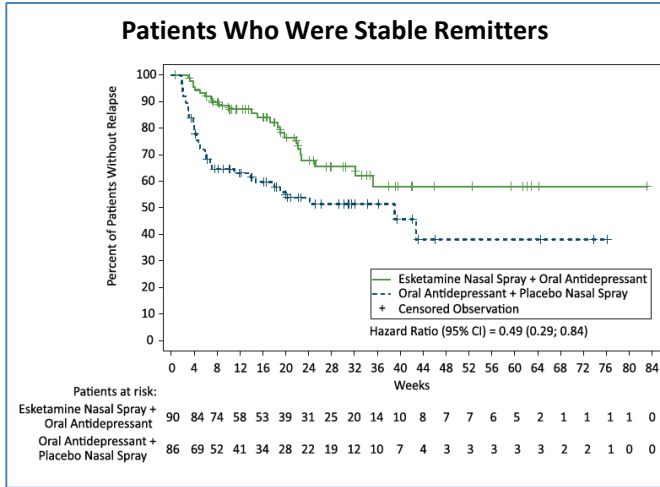


Stable Remitters: MADRS total score ≤ 12 for at least 3 of the last 4 weeks of the optimization phase, with MADRS total score missing once or >12 at week 13 or 14 permitted, and ≤ 12 at weeks 15 and 16 required.

Stable Responders: $\geq 50\%$ reduction in MADRS total score from baseline in the last 2 weeks of the optimization phase but who did not achieve stable remission criteria.

Stable remitters and stable responders were non-overlapping groups.

Esketamine Nasal Spray + Oral Antidepressant Significantly Delayed Relapse vs Oral Antidepressant + Placebo



AD = anti-depressants; ESK = esketamine; HR: hazard ratio; NS = nasal spray; PBO = placebo

Relapse Event :

ESK NS + Oral AD: 26.7%

Oral AD + PBO NS: 45.3%

51% reduction
(HR: 0.49; 95% CI: 0.29, 0.84; P=0.003)

Median Time to Relapse:

ESK NS + Oral AD: Not Estimable

Oral AD + PBO NS: 273 days

Relapse Event :

ESK NS + Oral AD: 25.8%

Oral AD + PBO NS: 57.6%

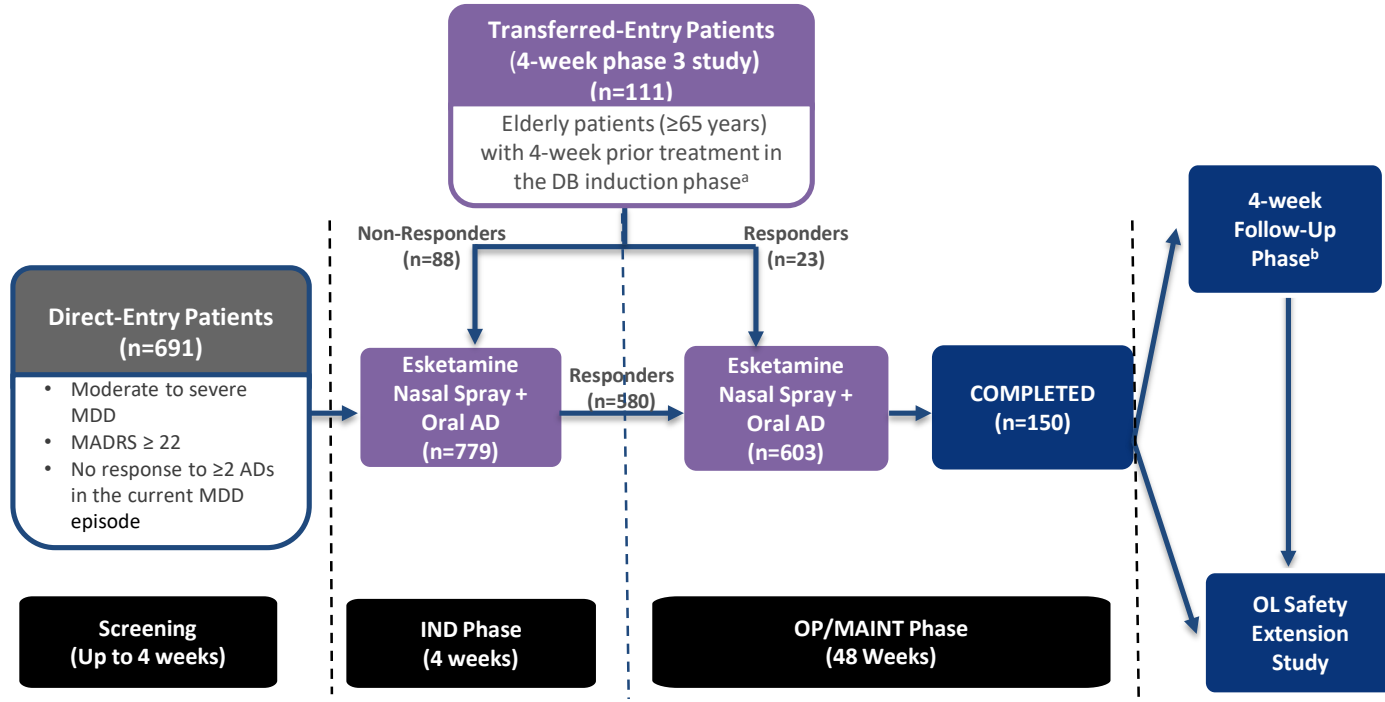
70% reduction
(HR: 0.30; 95% CI: 0.16, 0.55; P <0.001)

Median Time to Relapse:

ESK NS + Oral AD: 635 days

Oral AD + PBO NS: 88 days

SUSTAIN-2 (3004) Study Design



Note: The esketamine nasal spray 28 mg dose was used only in patients ≥65 years of age. At entry to the present study, transferred-entry patients continued to receive the same oral AD initiated in the short-term phase 3 study. A new oral AD medication was initiated only in the direct-entry patients.

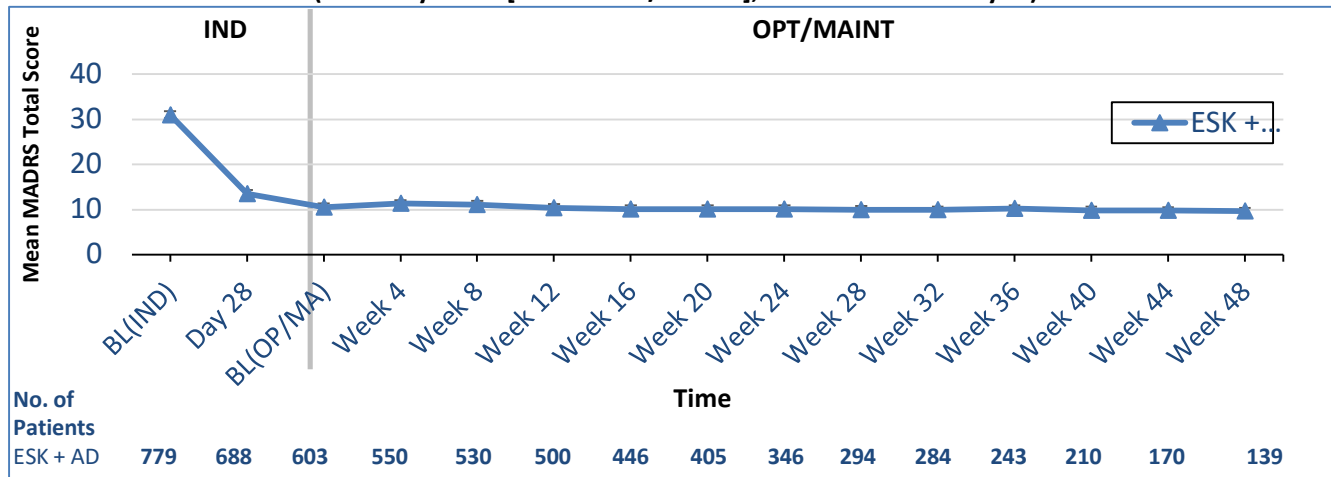
^aResponders and non-responders were regardless of treatment group; ^bNonresponders from the IND phase, discontinued patients from both treatment phases, or patients who completed the OPT/MAINT phase entered the follow-up phase.

AD = antidepressant; IND = induction phase; MADRS, Montgomery-Asberg Depression Rating Scale; MDD = major depressive disorder; OL = open-label; OP/MAINT = optimization/maintenance phase.

Wajs E, et al. Poster presented at *the European College of Neuropsychopharmacology (ECNP) Congress*; October 7, 2018; Barcelona, Spain.

Response Increased During the Induction Phase and Remained Stable Over Time

Mean Montgomery-Asberg Depression Rating Scale Total Score Over Time
(full analysis set [IND and OP/MAINT]; observed case analysis)



IND Endpoint:

Responders: 78.4%

(593/756)

Remitters: 47.2% (357/756)

OP/MAINT Endpoint:

Responders: 76.5% (461/603)

Remitters: 58.2% (351/603)

Responders ($\geq 50\%$ reduction in the MADRS total score); Remitters (MADRS total score ≤ 12)

Full analysis sets: All patients who received ≥ 1 dose of nasal spray study medication or oral antidepressant in the open-label IND or OP/MAINT phases.

AD = oral antidepressant; ESK = esketamine; IND = induction phase; MADRS = Montgomery-Asberg Depression Rating Scale; OP/MAINT = optimization/maintenance phase; SE = standard error.



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Summary

Long-Term Studies

- ✓ In study 3003, continued treatment with esketamine plus an oral AD demonstrated a statistically significantly longer time to relapse versus treatment with an oral AD plus placebo in patients who were in either stable remission or stable response after 16 weeks of treatment with esketamine plus an oral AD. The majority of AEs were mild to moderate, observed post dose on dosing days, and generally resolved in the same day.¹
- ✓ In study 3004, following a 4-week induction phase, long-term treatment with esketamine (weekly or biweekly dosing) together with a newly initiated oral AD was tolerable in adult patients with TRD including elderly (≥ 65 years) patients.²

Adverse Events of Interest

- ✓ Blood pressure increases^{2,4,5} and dissociative symptoms/perceptual changes¹⁻⁵ began shortly after the start of esketamine dosing, peaked at 40 minutes, and generally resolved by 1.5 hours.
- ✓ In study 3004, there were no reported cases of interstitial or ulcerative cystitis.²



Use in Special Populations

- Not recommended during pregnancy
- Is present in human milk
- Safety and efficacy of esketamine in pediatric patients have not been evaluated



Drug Abuse Potential

- Schedule III controlled substance
- Individuals with a history of drug abuse or dependence may be at greater risk for abuse and misuse
- May produce a variety of symptoms: anxiety, dysphoria, disorientation, insomnia, flashback, hallucinations, and feelings of floating, detachment and to be spaced out



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Dependence Potential

- Physical dependence reported with longterm use of ketamine
 - Withdrawal symptoms with intake of large doses of ketamine: craving, fatigue, poor appetite and anxiety
- No withdrawal captured up to 4 weeks after cessation of esketamine treatment



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Lessons Learned

- Start early
- Do your homework
- Review and understand policies and procedures
- Have a back up plan
- Get to know the staff and clinic



Questions



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